PATENT SPECIFICATION

811,717

Date of Application and filing Complete Specification July 20, 1955.

No. 21001/55.

Application made in United States of America on July 28, 1954.

Complete Specification Published April 8, 1959.

Index at acceptance:—Class 81(1), B2(C:G:H:L:N:P:R:S).

International Classification:—A61k.

COMPLETE SPECIFICATION

Improvements in or relating to Therapeutic Compositions

We, CHAS. PFIZER & Co., INC., a corporation organised under the laws of the State of Delaware, United States of America, of 11, Bartlett Street, Brooklyn, New York, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is concerned with new therapeutic compositions. In particular it is concerned with compositions containing a water-insoluble salt of penicillin as the principal active ingredient.

A variety of preparations have been described involving a water-insoluble salt of penicillin, such as procaine penicillin and dibenzylethylenediamine penicillin, as the principal active therapeutic agent. Many of these have proven to be very useful in the therapy of infectious diseases. Certain of these compositions consist of aqueous suspensions of the antibiotic or preparations designed to be suspended in water before intramuscular injection.

It has been found that when particularly finely divided particles of a water-insoluble penicillin salt, that is, particles having an average diameter of less than about 10 to 20 microns, are placed in aqueous suspension, there is a definite tendency for the finer fractions of these materials to adhere to the walls of the glass containers in which they are commonly bottled. This is true even though the walls of such containers are treated with such materials as silicones which tend to make the bottles clear draining.

There are other disadvantages to such preparations. There is a tendency towards the formation of non-uniform portions of the suspension, that is, the withdrawal of part of the suspension from a bottle may not result in the administration of an amount of penicillin in proportions to the volume used. Furthermore, many of the preparations having very fine particles display undesirably high viscosity which makes it difficult to withdraw and administer a definite amount of the antibiotic preparation to a patient. In addition, many aqueous suspensions of water-insoluble penicillin salts have, in the past, tended toward the formation of agglomerates which cause plugging of hypodermic needles and binding of the pistons within hypodermic syringes when attempts are made to use the suspensions. A still further problem is encountered with sedimentation, many suspensions tending to settle out upon standing to form a sludge which is difficult or impossible to resuspend.

It has now been found that these difficulties can be obviated by mixing with a water-insoluble salt of penicillin in finely divided form, polyvinylpyrrolidone in an amount from about 0.05 to 2.0% by weight of the water insoluble penicillin salt, lecithin in an amount of from about 0.2 to about 5.0% by weight of the water-insoluble penicillin salt, a parenterally acceptable water-soluble buffer in an amount of from about 0.5 to 10% by weight of the water-insoluble penicillin salt, an alkali metal salt of carboxymethyl cellulose in an amount of from about 0.1 to 3% by weight of the water-insoluble penicillin salt and a preservative, to obtain particularly excellent preparations in dry powdered form suitable for extemporaneous compounding with water to form aqueous suspensions.

It has further been found that particularly advantageous aqueous suspensions of enhanced stability may be provided by incorporating with these materials a proportion of a stable polyhydroxy alcohol.

In the preparation of the compositions of this invention, the use of a variety of water-insoluble salts of penicillin is contemplated, such as procaine penicillin; dibenzylethylenediamine penicillin; N-benzyl-N^1-(3-ethoxy-4-hydroxy)-benzyl-ethylenediamine penicillin; 2-chloroprocaine penicillin; and N,N^1-di-(4-methoxybenzyl)-ethylenediamine penicillin. Of these, procaine penicillin and dibenzylethylenediamine penicillin are particularly advan-

tageous. These salts are generally employed in an amount sufficient to furnish from about 300,000 to 600,000 units of penicillin per cc. of final suspension. In preparing dry penicillin compositions suitable for extemporaneous compounding with water, it is advantageous to employ finely divided penicillin, i.e., penicillin salts consisting substantially of particles ranging from about 5 to 30 microns in size, with preferably none in excess of 100 microns. It is preferred to employ particles having a size of from about 5 to 15 microns for preparations which are to be maintained in aqueous suspension over prolonged periods of time. Particles of this size are more readily suspended and maintained in stable suspension than are those of a coarser or finer particle size.

Polyvinylpyrrolidone (PVP) is a high molecular weight polymer formed by the polymerization of vinyl pyrrolidone by methods well known in the art. It is commercially available under the Registered Trade Mark " Plasdone ". For the purposes of this invention, polyvinylpyrrolidone, having a K value ranging from 26 to 36 is especially useful. The K value expresses the degree of polymerization of polyvinylpyrrolidone, and is calculated from the relative viscosity or ratio of the viscosity of a dilute solution of PVP (such as a 1% solution) to the viscosity of the solvent, i.e. water. A preferred form of polyvinylpyrrolidone exhibits a K value of 30, corresponding to an average molecular weight of 40,000. The polyvinylpyrrolidone exerts both a dispersing action on the penicillin, particularly procaine penicillin, and a stabilizing effect on the suspension. Thus, it facilitates the production of a uniform suspension of the water-insoluble penicillin and thereafter inhibits degradation of the penicillin. In this respect, it may be characterized as having a physico-chemical effect in the composition. An amount of polyvinylpyrrolidone of from about 0.05 to 2% by weight of the water-insoluble penicillin salts is used to accomplish the desired effects. This corresponds to a weight/volume proportion from about 0.02 to 0.6%, based on the final aqueous suspension. The preferred amount of polyvinylpyrrolidone is from about 0.1 to 1.5% by weight of the water-insoluble penicillin (approximately 0.03 to 0.45% on a wt./vol. basis).

The lecithin employed in this invention cooperates with the polyvinylpyrrolidone in dispersing the water-insoluble penicillin salts, and is especially useful in creating an interface which drains clear from the side walls of silicone treated containers. An amount of lecithin from about 0.2 to about 5% (0.06 to 1.5 wt./vol.%), preferably from about 1 to 3% (0.30 to 0.90 wt./vol.%) by weight of the water-insoluble penicillin salt is used for this purpose.

The buffer, in turn, stabilizes the resulting suspensions against the *p*H changes and thereby prevents degradation of the penicillin. While a variety of water-soluble, parenterally acceptable buffers may be used in this connection, it is preferred to employ an alkali metal salt of a polybasic organic acid, such as sodium citrate. Other suitable buffers include sodium acetate, sodium lactate and alkali metal salts of inorganic acids, such as monobasic and dibasic sodium phosphates. The buffer is employed in an amount of from about 0.5 to 10% by weight of the water-insoluble penicillin, i.e. 0.15 to 3.0 wt./vol.%.

Suitable preservatives include the following: " Parabens ", i.e., lower alkyl, such as methyl, propyl, and/or butyl esters of parahydroxybenzoic acid; sodium bisulfite; quaternary ammonium compounds such as benzalkonium chloride. The preservative is especially useful in multiple dose suspensions to protect the same against possible contamination which may be introduced to the suspension while preparing for injection. For this purpose, a minor amount of preservative such as from about 0.01 to 0.5% by weight of the water-insoluble penicillin (0.003 to 0.15 wt./vol.%) is generally adequate.

In those instances where a preservative is used to prevent the growth of possible contaminating organisms, there is a tendency for the preservative, particularly in the case of the parahydroxybenzoic acid esters, to create, in conjunction with the lecithin, a pronounced floculated condition of the water-insoluble penicillin, especially procaine penicillin. The addition of polyvinylpyrrolidone to such compositions has been found to be highly advantageous in controlling this flocculated condition to the point of desirable fluidity.

The alkali metal salt of carboxymethyl cellulose, such as sodium carboxymethyl cellulose, acts as a suspending agent for the dispersion formed by the polyvinylpyrrolidone and lecithin. The alkali metal salt of carboxymethyl cellulose apparently acts further to prevent the settling of the polyvinylpyrrolidone—and lecithin—produced dispersions, thereby resulting in a more stable suspension than is possible without such an agent. The alkali metal salt of carboxymethyl cellulose also assists the lecithin in promoting the desired drain-clear characteristics of the suspensions. These effects are readily obtained by employing from about 0.1 to 3% (0.03 to 0.90 wt./vol.%) of alkali metal salt of carboxymethyl cellulose by weight of the water-insoluble penicillin.

In some instances, it may also be advantageous to supplement the above-described ingredients with a proportion of a stable polyhydric alcohol, such as sorbitol (1,2,3,4,5,6,-hexanehexol) and its isomer mannitol in an amount of from about 25 to 85% (7.50 to 25.50 wt./vol.%) preferably 35 to 65% (10.50 to 19.50 wt./vol.%) by weight of the water-

insoluble penicillin. The polyhydric alcohol functions as a diluent extender replacing some of the water in the system and thereby raising the specific gravity thereof to decrease the sedimentation rate of the suspended particles. In this respect, the polyhydric alcohol augments the polyvinylpyrrolidone in stabilizing the penicillin suspensions, particularly the suspensions of procaine penicillin.

If lecithin is omitted from the compositions of this invention, the suspensions obtained are not nearly as desirable. There is a definite tendency to form films on the walls of the bottles in which the suspension is stored and a non-uniform suspension is often encountered, even if samples are withdrawn shortly after violent agitation. In like manner, the omission of polyvinylpyrrolidone from the compositions results in suspensions that are not nearly as effective as when the compositions of the invention are used. The preparations of this invention display a remarkably high order of stability even when the water-insoluble suspension is prepared and stored for extended periods of time. There is no tendency for the formation of scum resulting from decomposition products which occur in the absence of any of the components of these compositions.

The compositions of this invention are particularly effective in giving a prolonged therapeutic blood level upon intramuscular administration. Certain other materials may be included in order to increase the value of the compositions. However, these are not essential for the proper functioning of the compositions. For instance, the use of a water-soluble salt of penicillin in addition to the water-insoluble salt assists in obtaining a rapid rise in penicillin blood level upon administration of the compositions. There may be also included in the compositions a minor proportion of procaine hydrochloride as a solubility depressant, that is, less than about 5% by weight based on the suspension volume (5% wt./vol.%), when procaine penicillin is the water-insoluble penicillin salt. Similarly, a small amount of dibenzylethylenediamine diacetate may be included in aqueous suspensions or in dry compositions for the preparation of aqueous suspensions in which dibenzylethylenediamine penicillin is the principal active ingredient.

The following example is given by way of illustration and is not intended as a limitation of this invention:

EXAMPLE

Three hundred grams of procaine penicillin having an average particle size of less than about 15 microns were thoroughly dispersed, to provide 300,000 units of penicillin per millilitre, in an aqueous diluent containing sodium citrate 11.4 grams, methyl ester of parahydroxybenzoic acid 1.37 grams, propyl ester of parahydroxybenzoic acid 0.15 gram, lecithin 7.60 grams, polyvinylpyrrolidone (PVP) 0.76 gram (average molecular weight 40,000), and sodium carboxy methyl cellulose (CMC) 1.52 grams. The aqueous suspension thus prepared was then dispensed into multiple-dose glass bottles, placing in each sufficient material to provide 10 injections of 300,000 units per millilitre each. All of these operations were conducted under sterile conditions and the bottles were stoppered and capped. It was found that the aqueous suspension maintained excellent stability upon storage at room temperature for several months. No indications of scum or film formation were observed and a minimum of agitation after such storage resulted in a uniform suspension. The material was readily withdrawn through a 22 gauge hypodermic needle with no plugging of the needle and with considerable ease. Ten uniform proportions could be withdrawn from the bottle, leaving a very small amount of residual material. The product flowed freely from the walls of the glass vials and gave no evidences of adhering thereto.

WHAT WE CLAIM IS:—

1. A therapeutic penicillin composition comprising a water-insoluble salt of penicillin in finely divided form, polyvinypyrrolidone in an amount of from about 0.05 to 2.0% by weight of the water-insoluble penicillin salt, lecithin in an amount of from about 0.2 to about 5.0% by weight of the water-insoluble penicillin salt, a parenterally acceptable water-soluble buffer in an amount of from about 0.5 to 10% by weight of the water-insoluble penicillin salt, an alkali metal salt of carboxymethyl cellulose in an amount of from about 0.1 to 3% by weight of the water-insoluble penicillin salt and a preservative.

2. A composition according to Claim 1, in which the preservative is present in an amount of from about 0.01 to 0.5% by weight of the water-insoluble penicillin salt.

3. A composition according to Claim 1 or 2 in which the water-insoluble penicillin salt is procaine penicillin.

4. A composition according to any of Claims 1—3, in which the water-insoluble penicillin salt is dibenzylethylenediamine penicillin.

5. The therapeutic penicillin compositions substantially as set forth in the example.

6. A stable aqueous penicillin suspension formed from a composition according to any one of the preceding claims.

7. A suspension according to Claim 6, including a stable polyhydric alcohol such as sorbitol.

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Chartered Patent Agents,
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Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1959.
Published at The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.